

1146-114**Coronary Artery Disease in Patients With Multiple Emergency Department Visits and Negative Immediate Exercise Tests for Chest Pain: An Important Minority in a Total Cohort of Over 3,000 Low-Risk Patients Presenting With Chest Pain**

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Background: Low risk patients (pts) presenting to our emergency department (ED) with chest pain undergo immediate exercise testing (IET).

Methods: IET was performed in all low risk pts presenting to the ED with chest pain and results and clinical outcome were analyzed with particular reference to the group with multiple visits and negative IETs.

Results: Of 3,432 patients tested during a 7.5 year interval, IET was positive in 353 (10.3%), nondiagnostic in 830 (24.2%) and negative in 2,249 (65.5%). During the study period, 289 (13%) of the 2249 pts with negative tests had multiple (≥ 2) IET for chest pain. The total number of negative IET during the study period was 2,656 which were obtained in 1,960 pts with single IET and in the multivisit (MV) subgroup of 289 pts who had 696 negative IET. Thus, the MV subgroup comprised 13% (289/2,249) of all pts with negative IET but accounted for 26% (696/2656) of the total number of negative IET. In the MV subgroup (n=289), 261 (90.3%) pts had 2-3 IET and 28 (8.7%) had ≥ 4 IET. The mean number of IET in the MV subgroup = 2.7 (range 2-7). The MV negative subgroup was similar (p>0.05) in age (52 vs. 51 yr) and number of cardiac risk factors (1.5 vs. 1.5) to the single negative IET pts but the proportion of women was higher in MV (54% vs. 44%, p<0.05). In the MV negative IET pts, there was no cardiac mortality, 7 (2.4%) pts ultimately had myocardial infarction and after a mean of 3.7 tests, 25 underwent cardiac catheterization showing critical coronary artery disease and 24 (8.3%) of these pts had myocardial revascularization.

Conclusions: Although a minority of negative IET pts had multiple visits to the ED, they accounted for a disproportionate number of the IET by the entire negative group. An important minority of the MV negative subgroup was ultimately found to have coronary artery disease after multiple tests and were candidates for revascularization. Earlier definitive evaluation of MV pts could obviate repeat visits in many and afford appropriate therapy for coronary artery disease in an important minority.

ORAL CONTRIBUTIONS

849 Heart Failure, Basic Science, Animal Models, and Human StudiesTuesday, March 09, 2004, 2:00 p.m.-3:30 p.m.
Morial Convention Center, Room 217

2:00 p.m.

849-1**Uncoupling Proteins Shift During Cardiac Hypertrophy and Renin-Angiotensin System Suppression**

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Background: Improving energetics during heart failure may aid to preserve cardiac function. Uncoupling proteins (UCP) are key regulators of energetics in skeletal muscle and adipose tissue. They reduce the proton electrochemical gradient across the innermitochondrial membrane. However, their role in cardiac tissue is poorly understood. In mice with heart failure, increased UCP2 coincides with reduced high-energy phosphates. In humans, reduced UCP3 in failing hearts is normalized with left ventricular assist devices. RAAS suppression with angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor I (ATR1) blockers improve cardiac function and reduce remodeling. We asked if these benefits were associated with improved cardiac energetics.

Methods: We examined UCP1, UCP2, UCP3 mRNA levels (real-time RT-PCR) in thyroid-hormone (T3)-induced cardiac hypertrophy (C57BL/6 mice) and in mice given T3 plus an antiangiogenic drug, TNP-470 on 1-4, 14 d. We measured the effect of captopril or candesartan (14 d) on UCPs in C57BL/6 mice. Body, left/right ventricles, and atria weights and tibia length were assessed.

Results: T3-induced hypertrophy increased left ventricle (LV) UCP2 and UCP3 mRNA levels, and reduced UCP1. Compared to controls, UCP2 increased 5 fold (1, 2 d), 10 fold (3 d), and 20 fold (4 d) with no further increases despite continued LV increases (14 d). The UCP2 increases coincided with the most angiogenic phase (1-4 d) of T3-induced hypertrophy. We examined the effects of an antiangiogenic agent, TNP-470, on UCP shifts and hypertrophy. We treated mice with T3 plus TNP-470 (1, 4 d). TNP-470 reduced UCP2 to normal and limited increases in LV mass (T3: 117 ± 12 mg; T3+TNP-470: 94 ± 6.0 mg), but did not negate UCP3 or UCP1 shifts. In addition, mice given captopril or candesartan (14 d) had reduced UCP2 levels (2 fold) and LV weights (controls: 125 ± 10 ; captopril: 94 ± 4 ; candesartan: 95 ± 2 mg). UCP3 and UCP1 were unchanged.

Conclusion: UCPs may be important regulators of cardiac energetics. Perturbations may contribute to heart failure. Agents that normalize UCP expressions (ie: TNP-470, ACE inhibitors/ATR1 blockers) may improve cardiac function during hypertrophy and failure.

2:15 p.m.

849-2**Left Ventricular Assist Device Support Fails to Normalize the Beta-1/Beta-2 Adrenergic Receptor Ratio in Human Heart Failure**

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Background: Human heart failure is associated with a decreased response to beta-adrenergic stimulation due to a decrease in beta-adrenergic receptors, particularly a decrease in density of beta-1 receptors. During heart failure, the ratio of beta-1/beta-2 receptors is approximately 60/40, as compared to 80/20 in non-failing hearts. We have shown that following left ventricular assist device (LVAD) support of the failing heart, total receptor density recovers quickly, but recovery of the inotropic response to stimulation is delayed. This study tested the hypothesis that delayed recovery of inotropy is due to a delayed restoration in the ratio of beta-1/beta-2 adrenergic receptors.

Methods: Inotropic responsiveness to one micromolar isoproterenol was measured in isolated, isometrically contracting human trabecular muscles from tissue removed at LVAD implant and explant. Total beta receptor density were quantified in the same tissue pairs by Scatchard analysis using radiolabeled cyanopindolol, while receptor subtypes were determined by two-site competition binding curves using 15 doses of ICI 118,551.

Results: At time of LVAD explant, the inotropic response to isoproterenol was greater ($149 \pm 29\%$) as compared to the time of implant ($68 \pm 14\%$, p < 0.05), and the response continued to improve with increased duration of support (p < 0.05). Total receptor density was increased after LVAD (72.3 ± 7.8 vs 24.2 ± 3.6 fmol/mg protein; p < 0.0001), whereas the percent of beta-1 receptors was not different between the two groups ($64.4 \pm 6.1\%$ at implant; $68.4 \pm 2.0\%$ at explant). While the percent of beta-1 receptors was not changed, the absolute number of both beta-1 (50.3 ± 6.4 vs 19.4 ± 3.5 fmol/mg protein, p < 0.001) and beta-2 receptors (21.9 ± 2.2 vs 10.8 ± 2.6 fmol/mg protein, p < 0.05) was increased after LVAD.

Conclusion: Although the total density of beta-adrenergic receptors recovers following LVAD support of the failing human heart, the ratio of beta-1/beta-2 receptors remains at failing (60/40) rather than non-failing (80/20) levels. The larger percentage of beta-2 receptors after LVAD may contribute to delayed recovery of the inotropic response.

2:30 p.m.

849-3**Extracellular Matrix Remodeling During Left Ventricular Assist Device Support: Relation Between Collagen and Passive Pressure-Volume Relations**

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Introduction: Left ventricular assist device (LVAD) support of failing hearts induces reverse remodeling, manifest as shifts towards lower volumes of the passive pressure-volume relationship (PVR). This may be a consequence of regression of hypertrophy and/or changes in myocardial properties due to extracellular matrix remodeling. However, the relative contributions of these factors to reverse remodeling are unknown.

Methods: LV tissue samples were collected from idiopathic dilated cardiomyopathic (DCM) hearts at the time of cardiac transplantation in patients requiring (n=16) or not requiring (n=16) prior LVAD support and from 5 normal hearts not suitable for transplantation. Total collagen (hydroxyproline), soluble collagen and insoluble collagen were determined. Chamber capacitance and myocardial stiffness were calculated from *ex-vivo* PVRs and measured LV wall volume.

Results: Compared to normals, total collagen and soluble collagen were increased in DCM (3.1 ± 1.5 vs 6.1 ± 3.4 $\mu\text{g}/\text{mg}$, p=0.014; 1.4 ± 0.3 vs 4.1 ± 0.9 $\mu\text{g}/\text{mg}$, respectively, p<0.001). LVAD support further increased total collagen (9.0 ± 3.3 $\mu\text{g}/\text{mg}$, p=0.019 vs DCM), which was due to an increase of insoluble collagen (2.0 ± 3.0 vs 5.1 ± 3.1 $\mu\text{g}/\text{mg}$, p=0.008) with no change in soluble collagen (4.1 ± 0.9 vs 3.9 ± 1.0 , p=NS). LV mass was decreased by LVAD support (296 ± 73 vs 234 ± 60 g, p=0.014), the PVR shifted towards lower volumes with a chamber capacitance (volume at a pressure of 30 mmHg) decreasing from 266 ± 126 ml to 192 ± 87 ml (p=0.024). However, myocardial stiffness constant was not affected (9.9 ± 0.7 vs 10.6 ± 0.9 , p=NS).

Discussion: LVAD-support of the failing human heart leads to increased total collagen and cross-linking of collagen, suggestive of increased tensile strength of the extracellular matrix. Despite these changes, however, global myocardial stiffness constant was unaffected. These data lead to the provocative hypothesis that the profound changes induced by LVADs indicative of reverse structural remodeling are mainly due to regression of myocyte hypertrophy, with relatively little impact of the changes in collagen matrix on passive myocardial properties.

2:45 p.m.

849-4**Soluble Tumor Necrosis Factor Receptor (Etanercept) Treatment Enhances Left Ventricular Dysfunction in an Experimental Model of Chronic Chagas Disease Cardiomyopathy**

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Background: chronic Chagas' disease cardiomyopathy (CCC), caused by the protozoan *Trypanosoma cruzi*, affects ca. 3 million patients in Latin America. The lack of proven efficacious therapy is associated with worse prognosis of CCC. Chagas'disease is associated to increased production of proinflammatory cytokines such as TNF-alpha. The aim of this work was to evaluate Etanercept, a TNF-blocking agent, as a potential therapeutic approach in the control of CCC development. For that matter, we used as a model the